At page 2 after the second full paragraph, please insert a new paragraph as follows:

The Robert A. Welch Foundation, Houston, Texas, supported research related to the present invention through grant number I-1424.

Please replace the paragraph bridging page 2 and 3 with the following:

In one embodiment, the invention provides methods of detecting binding of a PAS domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of (a) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and (b) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. In a preferred embodiment, the recited PAS domain is PAS kinase PAS A.[[.]]

Please replace the last full paragraph on page 4 with the following:

This aspect of the invention provides methods and corresponding compositions, kits, instructions and business methods for detecting binding of a PAS domain with a foreign (i.e. not a natural ligand of the PAS domain) core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of (a) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and (b) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. In a preferred embodiment, the recited PAS domain is PAS kinase PAS A.

Please replace the first full paragraph on page 5 through the third full paragraph on page 6 with

the following:

This aspect of the invention provides methods and corresponding compositions, kits, instructions and business methods for changing a functional surface binding specificity of a PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent and/or no x-ray crystallographic-apparent a priori formed ligand cavity, the method comprising the steps of (a) introducing into the hydrophobic core of the PAS domain a ligand of the PAS domain such that the ligand stably and specifically binds [[in]] within the core; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain.

The recited binding specificity may be a change in intermolecular or intramolecular binding affinity of the PAS domain, such as an inter- or intramolecular PAS-PAS interaction, and may be manifested in a variety of functional changes, such as a change in kinase activity or specificity, a change in channel patency or specificity, etc. Targetable PAS domains are well-known to mediate and regulate a wide variety of functions, and we have found diverse, generalizable examples to be subject to the disclosed ligand regulation.

The PAS domain is typically part of a larger native protein comprising the PAS domain, and may be isolated or expressed by and within a host cell or animal, wherein the ligand is foreign to the host, and the change is conveniently detected indirectly or inferentially as a change in host cell or animal physiology precorrelated with the change in binding specificity. Targetable PAS domains are well-known to mediate and regulate a wide variety of functions which manifest themselves in a corresponding diversity of physiological readouts, and we have found diverse, generalizable examples to be subject to the disclosed ligand regulation. For example, point mutations in a potassium channel subject to PAS domain regulation are known to mediate certain heritable forms of heart disease, which mutations may be rescued by foreign ligand. Hence, the recited change in functional surface binding specificity may result in an inhibition, an enhancement or a restoration of activity or function, depending on the particular application.

Accordingly, a wide variety of suitable PAS domains may be targeted, including PAS kinase PAS A, NPAS2 PAS A, HIF2a PAS B, HIF1a PASB, ARNT PAS B and HERG terminal

PAS, which are typically present as part of their full-length natural proteins.

As exemplified below, suitable foreign ligands may be recovered or derived from a wide variety of source materials. Candidate ligands encompass numerous chemical classes, though typically they are organic compounds; preferably small organic compounds and are obtained from a wide variety of sources including libraries of synthetic or natural compounds. Conventional SAR analyses [[are]] provide ligands of higher affinity and/or specificity. In exemplary embodiments, the foreign ligands are derived from or are structurally similar to those shown below (e.g. Tables 1, 2 and 3).

Pharmaceutical compositions.

When targeting PAS domains expressed by and within a host cell or animal, the ligands are employed as pharmaceuticals, and the foreign PAS core ligands of this invention are typically administered in the form of a pharmaceutical composition comprising at least one active ligand and a carrier, vehicle or excipient suitable for use in pharmaceutical compositions.[[.]] Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, plasticizers, disintegrants, colorants, bulking substances, flavorings, sweeteners and miscellaneous materials such as buffers and adsorbents in order to prepare a particular medicated composition. Such carriers are well known in the pharmaceutical art as are procedures for preparing pharmaceutical compositions.

Please replace the last full paragraph on page 12 and the paragraph bridging page 12 and 13 with the following:

In yet further aspects, the invention provides a method of [[a]] modulating a binding activity of an immunophilin FK-506 binding protein (FKBP), the method comprising the steps of: (a) contacting the FKBP with a ligand selected from the group consisting of 2-phenylimidazole, KG-190, KG-720, KG-373 and KG-510; and (b) detecting a modulation of the binding activity of the FKBP.

In yet further aspects, the invention provides a method of [[a]] modulating a binding activity of a Rho GDP-dissociation inhibitor (GDI), the method comprising the steps of: (a)

contacting the [[FKBP]] GDI with a ligand selected from the group consisting of KG-406, KG-654 and KG-509; and (b) detecting a modulation of the binding activity of the GDI.

Please replace the paragraph bridging page 14 and 15 with the following:

A total of 8 hits with binding affinities better than 1 mM were found during our $^{1}H/^{15}N$-HSQC-based NMR screen (Figure 1). The map of residues with chemical shift changes (Dd) > 0.075 ppm, figure 2A (right), shows that compound KG-190 interacts with FKBP in the same region where FK-506 (shown ~~in magenta~~ shaded on the left) is bound in the crystal structure of the FKBP/FK-506 complex (Van Duyne et al., 1991). Using one-dimensional NMR methods it has previously been shown (Hajduk et al., 1997) that a compound related to KG-190, 2-phenylimidazole, selectively binds FKBP. Other hits from this screen interacted with the protein in a similar fashion but with lower affinities (scheme IA), demonstrating the ability of our library to identify a relevant binding site.

Please replace the second full paragraph on page 18 with the following:

Our structural studies confirm that core ligand binding in each HIF-2a PAS B and ARNT PAS B induces distal changes in PAS domain structure, and functional binding studies confirm resultant changes in DNA:HIF-2a:ARNT transcription complex formation and DNA binding specificity (e.g. Michel et al., Biochim Biophys Acta. 2002 Oct 11;1578(1-3):73-83). Table 3 show exemplary identified foreign ligands of HIF-2a PAS B and ANRT PAS B, respectively, which specifically bind within their hydrophobic cores and disrupt complex formation.